AR201-1393B

I. General Information

CAS Number: 563-80-4
Name: 2-Butanone, 3-methyl-
3-Methylbutanone
3-Methyl-2-butanone
2-Acetylpropane
2-Methyl-3-butanone
2-Methylbutan-3-one
Isopropyl methyl ketone
Methyl isopropyl ketone
MIPK

II. Physical-Chemical Data

A. Melting Point

Test Substance	
Test substance:	MIPK
Remarks:	
Method	
Method:	Estimation
Remarks:	
Results	
Melting point value:	-79.46 °C
Remarks:	
References	MPBPWIN v1.31; Meylan, W. (1993). User's Guide for the Estimation Programs Interface (EPI), Version 3.01, Syracuse Research Corporation, Syracuse, New York 13210.
Other	

B. Boiling Point

Test Substance	
Test substance:	MIPK
Remarks:	
Method	
Method:	Estimation
Remarks:	Method was noted to have been an adaptation of Stein & Brown
Results	
Boiling point value:	80.27 °C
Remarks:	
References	MPBPWIN v1.31; Meylan, W. (1993). User's Guide for the Estimation Programs Interface (EPI), Version 3.01, Syracuse Research Corporation, Syracuse, New York 13210.
Other	

C. Vapor Pressure

Test Substance	
Test substance:	MIPK
Remarks:	
Method	
Method:	Estimation
Remarks:	Mean of Antoine and Grain methods
Results	
Vapor pressure value:	95.5 mmHg
Temperature:	25 ^{o}C
Remarks:	
References	MPBPWIN v1.31; Meylan, W. (1993). User's Guide for the Estimation Programs Interface (EPI), Version 3.01, Syracuse Research Corporation, Syracuse, New York 13210.
Other	

D. Partition Coefficient

Test Substance	
Test substance:	MIPK
Remarks:	
Method	
Method:	Estimation
Remarks:	
Results	
Log K_{OW}:	0.67
Remarks:	The EPIWIN database had a listed value of 0.84.
References	KOWIN v1.63; Meylan, W. (1993). User's Guide for the Estimation Programs Interface (EPI), Version 3.01, Syracuse Research Corporation, Syracuse, New York 13210.
Other	

E. Water Solubility

Test Substance	
Test substance:	MIPK
Remarks:	
Method	
Method:	Estimation
Remarks:	
Results	
Value:	2,436 mg/L
Temperature:	25 ^{o}C
Description:	Slight (1-10 g/L)
Remarks:	A K_{ow} of 0.84 was used in the estimation
References	WSKOW v1.33; Meylan, W. (1993). User's Guide for the Estimation Programs Interface (EPI), Version 3.01, Syracuse Research Corporation, Syracuse, New York 13210.
Other	

III. Environmental Fate Endpoints

A. Photodegradation

Test Substance	
Test substance:	MIPK
Remarks:	
Method	
Method:	Estimation
Test type:	Atmospheric oxidation
Remarks:	
Results	
Temperature:	25 ^{o}C
Hydroxyl radicals reaction	
OH Rate constant:	2.6178 x 10^{-12} cm^3/molecule-sec
Half-life	4.086 Days (12-hr day; 1.5x10^6 OH/cm^3)
Ozone reaction:	No ozone reaction estimation
Remarks:	
Conclusions	Material is oxidized by atmospheric hydroxyl radicals at a slow rate.
Data Quality	
Remarks:	
References	AopWin v1.88; Meylan, W. (1993). User's Guide for the Estimation Programs Interface (EPI), Version 3.01, Syracuse Research Corporation, Syracuse, New York 13210.
Other	

B. Stability in Water

Reactivity of Selected Ketones With Water

This report has been prepared Dr. Paul Worsham of Eastman Chemical to document the known chemistry relevant to the stability of selected ketones in aqueous solution. The specific ketones addressed in this document are methyl propyl ketone (MPK; CAS# 107879), methyl isopropyl ketone (MIPK; CAS# 563804), methyl isoamyl ketone (MIAK; CAS# 110123), and methyl n-amyl ketone (MAK; CAS#110430).

Of particular concern in the evaluation of the stability of organic compounds in aqueous solution is the potential for hydrolysis. Hydrolysis is the reaction between water and an organic substrate resulting in the cleavage of existing chemical bonds and subsequent or simultaneous formation of new chemical bonds to form a different chemical compound. Typically, hydrolysis reactions involve incorporation of a water molecule into the structure of the reaction products. For organic substances that participate in hydrolysis reactions, various kinetic methods can be used to monitor the changes in concentration of reactants and determine the rate of transformation of the original substrate into reaction products. OECD Guideline 111 describes one such procedure for measuring the hydrolysis rate of water-soluble substrates as a function of pH. Substrates that exhibit high rates of hydrolysis are considered unstable in an aqueous environment.

Ketones as a class, and specifically the ketones identified above, do not participate in hydrolysis reactions. These ketones do not possess labile leaving groups that can be displaced by the nucleophilic attack of a water molecule, as is required in the mechanism of many hydrolysis reactions. Thus, it would not be meaningful to attempt to measure a hydrolysis rate using a protocol such as OECD Guideline 111.

Certain ketones may add water to form a hydrate under aqueous conditions, especially in the presence of mild acid; but, this addition is an equilibrium reaction that is reversible upon a change in water concentration, and the reaction ultimately leads to no permanent change in the structure of the ketone substrate.[1, 2]

A significant property of most ketones is that the hydrogen atoms on the carbons next to the carbonyl group are relatively acidic when compared to hydrogen atoms in typical hydrocarbons. Under strongly basic conditions these hydrogen atoms may be abstracted to form an enolate anion. This property allows ketones, especially methyl ketones such as the four ketones above, to participate in condensation reactions with other ketones and aldehydes. This reaction is called an aldol reaction and generates a higher molecular weight ketone having a hydroxyl group at the site of attack by the enolate anion. This type of condensation reaction is favored by high substrate concentrations and high pH (greater than 1 wt% NaOH). It is conceivable that some alkyl ketones, especially methyl ketones, could participate in aldol reactions in dilute aqueous solution at pH of 9 or higher. But, these reactions would be expected to be slow at ambient temperature, and the equilibrium for condensation of two ketones is unfavorable for aldol product formation[3]. Also, formation of the aldol product is reversible unless dehydration of the aldol occurs. Dehydration of an aldol intermediate in aqueous solution at ambient temperature also would be very slow.

Based on the properties of ketones described above one must conclude that MPK, MIPK, MIAK, and MAK are not subject to hydrolysis, but may participate in other transformations that convert the ketone to higher molecular weight compounds. These reactions would be expected to be very slow at mild temperatures and moderate pH. Therefore, it is my conclusion that MPK, MIPK, MIAK, and MAK should be considered stable in aqueous solution at temperatures and pH levels relevant to environmental and human exposure.

References:

(1) Bell and Clunie, *Trans. Faraday Soc.*, **48,** 439, (1952).
(2) Cohn and Urey, *J. Am. Chem. Soc.*, **60**, 679 (1938).
(3) March, J., ed. "Advanced Organic Chemistry", 3rd edition, p. 831, John Wiley & Sons, New York, 1985.

C. Biodegradation

Test Substance	
Test substance:	MIPK
Remarks:	Purity was 99.6%
Method	
Method:	OECD TG-301D
Test type:	Ready Biodegradability by the Closed Bottle Method
GLP:	Yes
Year:	2001
Contact time:	28-Days
Inoculum:	Activated sludge collected from Wareham, MA wastewater treatment plant
Remarks:	Benzoic acid at 10 mg/ml was used as a reference control. MIPK was assessed at a nominal concentration of 2.5 mg/L. Test vessels of 300ml BOD bottles were prepared per treatment (reference, test substance and inoculum blank), two each for Day 0 and three per sampling interval (Days 7, 14, 21, and 28). After the bottles were filled they were closed and wrapped in tin foil.
Results	
Degradation % at test end:	85% (>60% by Day 14)
Classification:	Readily biodegradable
Remarks:	Benzoic acid reference was degraded 84%. The temperature of the environment ranged from 20-24 ^{o}C. Dissolved oxygen concentrations in the control blank ranged from 9.1 mg/L on Day 0 to 7.8 mg/L on Day 28.
Conclusions	Material is considered readily biodegradable under the conditions of this test.
Data Quality	
Remarks:	This was a well-documented OECD guideline study conducted under GLP assurances.
References	Methyl Isopropyl Ketone – Determination of the Ready Biodegradability of a Test Substance by the Closed Bottle Method; Springborn Laboratories, Inc Wareham, MA Study No. 1852.6178, August 7, 2001.
Other	

D. Transport between Environmental Compartments (Fugacity)

Test Substance	
Test substance:	MIPK
Remarks:	
Method	
Test type:	Estimation
Model used:	Level III Fugacity Model; EPIWIN: EQC from Syracuse Research Corporation
Remarks:	
Results	
Model data and results:	Concentration (%)
Estimated distribution and media concentration (levels II/III):	Air 12.2 Water 49.4 Soil 38.3 Sediment 0.0633 Physical chemical values and estimated half-life values utilized in this model were default values obtained from the EPIWIN program.
Remarks:	
Data Quality	
Remarks:	
References	Meylan, W. (1993). User's Guide for the Estimation Programs Interface (EPI), Version 3.01, Syracuse Research Corporation, Syracuse, New York 13210. The Level III model incorporated into EPIWIN is a Syracuse Research Corporation adaptation of the methodology described by Mackay *et al.* 1996; *Environ. Toxicol. Chem.* **15(9)**, 1618-1626 and *Environ. Toxicol. Chem.* **15(9)**, 1627-1637.
Other	

IV. Ecotoxicity

A. Acute Toxicity to Fish

Test Substance	
Test substance:	MIPK
Remarks:	Purity was not available
Method	
Method:	Other
Test type:	Static
GLP:	No
Year:	1988
Species/strain:	Fathead minnow (*Pimephales promelas*)
Analytical monitoring:	Yes; Exposure solutions, temperature, pH, dissolved oxygen
Exposure period:	96-Hour
Remarks:	Water was filter-treated lake water with residual chlorine chemically removed. 10 fish per concentration level were used. Test was conducted in replicate at each concentration in glass containers. The biological loading was kept below 1.0 g wet wt./L. Exposure solutions were submitted for temperature, dissolved oxygen, and pH concentration determinations at 0, 24, 48, 72, and 96 hrs. Observations for stress and mortality were conducted at 0, 6, 24, 48, 72, and 96 hours.
Results	
Nominal concentration:	100 mg/L
Endpoint value:	LC_{50} >100 mg/L
Biological observations:	All control behavior was normal. One exposed fish was noted to exhibit depressed activity at 24-hours, all were normal at 48 hours, one was found dead between the 48 and 72 hour period and one was noted to be near death at 96-hours.
Statistical methods:	NA; Only one mortality was noted out of 20
Remarks:	Exposure temperature ranged from 20-21 ^{o}C, pH ranged from 7.7 to 8.4, and dissolved oxygen ranged from 5.4 to 8.9 mg/L. Solutions were gently aerated at 72 hours when the oxygen levels became depressed.
Conclusions	The LC_{50} value indicates that the test substance would not be classified according to the European Union's labeling directive and would correspond to a "low concern level" according to the U.S. EPA's assessment criteria.
Data Quality	
Reliability:	Reliable with restrictions
Remarks:	Study lacked some basic information as well as data indicating test material purity and analytical conformation of test concentrations.
References	An Acute Aquatic Effects Test with the Fathead Minnow (*Pimephales promelas*); Environmental Sciences Section, Health and Environment Laboratories, at Eastman Kodak Company, Rochester, NY; HAEL No. 88-0008; June 8, 2000.
Other	

B. Acute Toxicity to Aquatic Invertebrates

Test Substance	
Test substance:	MIPK
Remarks:	Purity was not available
Method	
Method:	Other
Test type:	Acute immobilization, Static
GLP:	No
Year:	1988
Species/strain:	Daphnid/*Daphnia magna*
Analytical monitoring:	Yes; Exposure solutions, temperature, pH, dissolved oxygen
Exposure period:	48-Hour
Remarks:	Water was filter-treated with residual chlorine chemically removed. 10 Daphnids per dose level were used. Test was conducted in replicate at each concentration in glass containers. Exposure solutions were submitted for temperature, dissolved oxygen, and pH concentration determinations at 0, 24, and 48 hrs. Observations for stress and mobility were conducted at 0, 6, 24, and 48 hours.
Results	
Nominal concentration:	100 mg/L
Endpoint value:	EC_{50} (48-hr) >100 mg/L
Biological observations:	The *Daphnia* exhibited behavior comparable to controls at 24 hours, but at 48-hours many were noted to be positioned at the surface.
Statistical methods:	NA; No significant differences in immobility were noted between treated and control Daphnids.
Remarks:	Exposure temperature ranged from 20-21 ^{o}C, pH ranged from 8.0 to 8.4, and dissolved oxygen ranged from 6.8 to 8.9 mg/L.
Conclusions	The EC_{50} value indicates that the test substance would not be classified according to the European Union's labeling directive and would correspond to a "low concern level" according to the U.S. EPA's assessment criteria.
Data Quality	
Reliability:	Reliable with restrictions
Remarks:	Study lacked some basic information as well as data indicating test material purity and analytical conformation of test concentrations.
References	An Acute Aquatic Effects Test with the Daphnid (*Daphnia magna*); Environmental Sciences Section, Health and Environment Laboratories, at Eastman Kodak Company, Rochester, NY; HAEL No. 88-0008, June 8, 2000
Other	

C. Toxicity to Aquatic Plants

Test Substance	
Test substance:	MIPK
Remarks:	Purity was 99.6%
Method	
Method:	OECD: TG-201
Test type:	Growth inhibition of algae
GLP:	Yes
Year:	2001
Species/strain:	*Selenastrum capricornutum*
Endpoint basis:	Cell concentrations (biomass) and growth rate
Exposure period:	72-hours
Analytical procedures:	Temperature, light intensity, rpm, and test substance concentration were assessed at the 0, 24, 48, and 72 hours. The pH was assessed at time 0 and after 72 hours.
Remarks:	
Results	
Nominal concentration:	7.8, 15.6, 31.3, 62.5, and 125.0 mg/L
Measured concentration:	4.1, 7.5, 14.8, 29.5, and 61.8 mg/L (geometric mean over all time points)
Endpoint value:	The estimated E_bC_{50} (0-72 hr) was 34.0 mg/L; the E_rC_{50} (0-72 hr) was 44.2 mg/L
NOEC:	The 72 hr NOEC was estimated to be 14.8 mg/L
Biological observations:	No deformed cells were noted
Was control response satisfactory:	Yes (culture concentrations increased by a factor of 93-fold)
Statistical methods:	EC_{50} and NOEC values were determined through use of SAS statistical software program AL_ACUTE (Ver. 2.2).
Remarks:	A mean illumination of 719.5 foot-candles was maintained. The mean culture temperature was 24°C and pH ranged from 7.5 to 9.0. Cultures were oscillated at 100 rpm. The significant loss (up to 78.2% over the course of the study) in test material was attributed to volatilization. No protocol deviations were noted.
Conclusions	The 72-hour E_bC_{50} and E_rC_{50} values indicate that, based on this study, the test substance would be classified as "harmful to aquatic organisms" according to the European Union's labeling directive and would be classified in a "moderate concern level" according to the U.S. EPA's assessment criteria.
Data Quality	
Reliability:	Reliable without restrictions
Remarks:	This was a well-documented OECD guideline study conducted under GLP assurances.
References	A Growth Inhibition Test with the Alga, *Selenastrum capricornutum*; Environmental Sciences Section, Health and Environment Laboratories, Eastman Kodak Company, Rochester, NY; Laboratory Project ID: EN-512-903146-A; July 11, 2001.
Other	

V. Toxicological Data

A. Acute Toxicity

Test Substance	
Test substance:	MIPK
Remarks:	Purity unknown
Method	
Method:	Acute lethality; Other
Test type:	LD_{50} estimate
GLP:	Yes
Year:	1988
Species/strain:	Rat/Crl:CD® (SD)BR
Sex:	Both
Animals/dose:	5
Vehicle:	Undiluted
Route of exposure:	Oral
Remarks:	Animals weighing 125-140 g (males) and 130-148 g (females) were administered doses of MIPK at a rate of 1,250, 2,500, and 5000 mg/kg. Animals were monitored for 14 days before being euthanized, dissected, and examined grossly. The LD50 estimate was determined by the Weil method.
Results	
Value:	LD_{50} = 3,078 mg/kg (both sexes)
Deaths at each dose:	1,250: none; 2,500: 2 (1/sex); 5,000: 10 (5/sex)
Remarks:	1,250 and 2,500 mg/kg: Clinical signs seen included slight to moderate weakness and ataxia in all animals shortly after dosing. All recovered after 24 hours and gained weight. None exhibited any gross pathological changes at necropsy. 5,000 mg/kg: Clinical signs included slight to severe weakness, ataxia, and prostration in all animals on day of dosing, with 2 males and 3 females dying within 4 hours. The remaining animals were found dead on next day. The only gross observation noted at necropsy was seen in those animals that died very shortly after dosing and consisted of test material in the GI tract. The exact cause of death was not determined in any animal.
Conclusions	Material is considered slightly toxic
Data Quality	
Reliability:	Reliable without restrictions
Remarks:	Although test article purity was not given, this is a well-documented study conducted under GLP assurances.
References	Acute toxicity of methyl isopropyl ketone, Toxicological Sciences Laboratory, Health and Environment Laboratories, Eastman Kodak Company, Rochester, NY; HAEL No. 88-0008, May 19, 1988.
Other	

Test Substance	
Test substance:	MIPK
Remarks:	Purity was >98%
Method	
Method:	Acute lethality; Other
Test type:	LC_{50} estimate
GLP:	Yes
Year:	1987
Species/strain:	Rat/Crl:CD® (SD)BR
Sex:	Both
Animals/sex/dose:	5
Route of exposure:	Inhalation
Remarks:	Males were 7 weeks old and weighed 252 g, while females were 9 weeks of age and weighed 201 g on average. Animals were exposed to MIPK using whole-body chambers for 6 hours at nominal concentrations of 0, 4,000, 6,000, or 9,000 ppm. Actual measured levels were 4,026, 5,708, and 8,270 ppm. After exposure, animals were monitored for clinical observations and weight change for 14-days prior to being euthanized.
Results	
Value:	LC_{50} (6-hr) = 6,377 ppm (22,464 mg/m^3) average of both sexes
Deaths at each dose:	4,000: 0/10; 6,000: 3/10 (1M, 2F); 9,000: 9/10 (5M, 4F)
Remarks:	During the exposure phase (Day 0) all animals in all groups exhibited severe CNS depression, lacrimation and dose-dependent hypoventilation. After exposure on Day 0 all animals exhibited minor lethargy to severe CNS depression and minimal to severe lacrimation. Sialorrhea was exhibited in one female exposed to 4,000 ppm. One of each sex at the 6,000 ppm level and all 5 males and 2 females exposed to 9,000 ppm died shortly after exposure on Day 0. The next day, one female each from the mid and high groups continued to show lethargy, poor body condition, and lacrimation. Piloerection was noted in all surviving animals in the 6,000 ppm group. Two females in the 9,000 ppm group died on Day 1. On Day 2, one female in the 6,000 ppm group died; the sole surviving female in the 9,000 ppm group showed lethargy, piloerection, gait disturbance, and ataxia. On Day 3 this animal had weight loss in addition to an unkempt and yellowed haircoat. Weight gains in those surviving exposure were minimal to negative during Day 1-3 but after three days all showed sustained gains and by Day 14 all groups were comparable to controls. The exact cause of death was not determined in any animal and no gross pathological changes were seen in any animal dying prematurely or at Day 14.
Conclusions	
Data Quality	
Reliability:	Reliable without restrictions
Remarks:	This is a well-documented study conducted under GLP assurances.
References	Acute inhalation toxicity study of methyl isopropyl ketone in the rat, Toxicological Sciences Laboratory, Health and Environment Laboratories, Eastman Kodak Company, Rochester, NY; HAEL No. 86-0157, June 8, 1987.
Other	

B. Repeated Dose Toxicity

Test Substance	
Test substance:	MIPK
Remarks:	Purity was 99.4%
Method	
Method:	Comparable to OECD-412, and EEC Annex V.B.8
Test type:	Repeated exposure
GLP:	Yes
Year:	1981
Species/strain:	Rat/CRL:CD®(SD)BR
Route of exposure:	Inhalation
Duration of test:	28-Days
Exposure levels:	0, 750, 1,500, 3,000 ppm
Sex:	Both
Exposure period:	6 hours/day
Frequency of treatment:	5 days/week
Control group and treatment:	Controls were exposed to room air.
Post-exposure observation period:	None
Remarks:	Rats (5/sex/dose) weighing 199 g (M) and 181 (F) were randomly assigned to each of the exposure groups. Animals were exposed using whole-body chambers and given feed *ad libitum* only during non-exposure periods. Body weights were recorded on Days 0, 4, 7, 14, 21, and 28 and clinical observations were made before and after exposure each day. At necropsy, complete hematology and clinical chemistry parameters were assessed and a full assortment of tissues were harvested for histological assessment and included nasal passages, trachea, lungs, heart, aorta, esophagus, stomach, duodenum, jejunum, ileum, cecum, colon, rectum, pancreas, liver, salivary glands, kidneys, urinary bladder, pituitary gland, adrenal gland, thyroid gland, parathyroid, thymus, spleen, mesenteric lymph nodes, bone marrow, brain, testes, epididymides, male accessory sex glands, ovaries, vagina, uterus, and Fallopian tubes.
Results	
NOAEL:	A NOEL was not determined due to presence of clinical effects during the exposure period. These effects rapidly dissipated during the post exposure period. No evidence of systemic toxicity was seen at 750 ppm (2,642 mg/m^3) and the LOAEL (based on weight loss) was 1,500 ppm (5,284 mg/m^3).
Actual exposure levels:	730, 1,488, 2,958 ppm

Toxic responses by dose:	No mortalities were observed in this study. Mean body weights were, in general, decreased in a dose dependent manner with it being statistically significant at Day 28 in the 1,500 and 3,000-ppm animals only. Both sexes exhibited dose-dependent lethargy (all dose levels) or moderate to severe narcosis (3,000 ppm) during most exposures. Excessive lacrimation was noted in all animals during the first exposure and then once thereafter in the 750 ppm group or on several occasion in one or more animals at the two higher levels. Animals in the 3000 ppm group also exhibited gait disturbances. Sialorrhea was noted on in 1-2 animals across all dose levels on occasion. All clinical signs rapidly diminished post-exposure and were not observed in the next day's pre-exposure observations. No changes in hematology or clinical chemistry parameters were observed that were considered to be related to test article exposure. Trends for an increase in several organ weights were noted, but statistical significance was only seen when compared on a relative to body weight basis and only at the two highest dose levels where reductions in body weight was also manifested. Absolute organ weight increases were noted in the adrenal gland of males and the livers of females, both only occurred at the highest exposure level and were seen in both sexes. Males at all levels showed evidence of hyaline droplet formation with a significant increase in its severity associated at the 1500 and 3000 ppm level. No histopathological changes were seen in females at any exposure level.
Statistical methods:	All continuous data were evaluated using computer generated statistical test: Bartlett's Test, One-way ANOVA, and Duncan's multiple range test. In cases of unequal variances a two-tailed t-test was employed. Selected pathology data were evaluated using contingency table analysis. Tests of independence and measures of association were done on two-way tables using the likelihood ratio Chi-square statistic. Multi-way tables were analyzed using log-linear models and the likelihood ratio Chi-square statistic. Significant effects were further examined using Dunnett's t-test.
Remarks:	
Conclusions	In general test material was well tolerated with the primary effect being a non-specific decrease in body weight at the highest two doses. A possible cause of this could be a decrease in food consumption related to the time needed to recover from the exposure-induced depression effects. (Unfortunately food intake was not measured to validate this hypothesis.) Although clinical signs of toxicity were seen at all levels, they rapidly diminished after exposure cessation. Furthermore, there was minimal evidence of any target organ toxicity based on changes in absolute organ weights and normal histological appearances. Hyaline droplet formation is not relevant to humans.
Data Quality	
Reliability:	Reliable with restrictions
Remarks:	This study was conducted using established protocols and GLP assurances.
References	Four Week Inhalation Toxicity Study of Methyl Isopropyl Ketone in the Rat. Toxicological Sciences Laboratory, Health and Environment Laboratories, Eastman Kodak Company, Rochester, NY; HAEL No. 88-0008, June 28, 1989.
Other	

C. Genetic Toxicity – Mutation

Test Substance	
Test substance:	MIPK
Remarks:	Purity was 99.6%
Method	
Method:	OECD:TG-471
Test type:	*In vitro* mutagenicity
GLP:	Yes
Year:	2001
Species/strain:	*Salmonella typhimurium*/TA98, 100, 1535, 1537, and *Escherichia coli*/WP2*uvr*A
Metabolic activation:	Yes; Aroclor 1254-induced SD rat liver S9
Concentration tested:	Maximum concentration tested was 5000 ug/plate
Remarks:	Positive controls (benzo[a]pyrene, 2-aminoanthracene, 2-nitrofluorene, sodium azide, 2-aminoanthracene, ICR-191, and 4-nitroquinoline-N-oxide) were run concurrently. DMSO was used as a vehicle control. Test material was evaluated in triplicate at each dose level.
Results	
Result:	No positive responses were induced in any of the tester strains
Cytotoxic concentration:	>5000 ug/plate (no evidence of cytotoxicity was seen)
Precipitation concentration:	No precipitate was noted at the highest concentration tested.
Genotoxic effects	
With activation:	Negative
Without activation:	Negative
Statistical Methods:	Mean number of revertants and standard deviations were calculated. Various criteria were established to constitute a valid assay and a positive response was indicated by a 2-3 fold increase in mean revertant number dependent on the bacterial tester strain.
Remarks:	All criteria for a valid study were met.
Conclusions	Material was not genotoxic under conditions of this assay.
Data Quality	
Reliability:	Reliable without restrictions
Remarks:	This was a well-documented OECD guideline study conducted under GLP assurances.
References	Covance Laboratories Inc., Vienna, VA; Study No.: 23080-0-409OECD; February 7, 2002.
Other	

D. Genetic Toxicity – Chromosomal Aberrations

Test Substance	
Test substance:	MIPK
Remarks:	Purity was 99.6%
Method	
Method:	OECD: TG-473
Test type:	*In vitro* mammalian chromosomal aberrations assay
GLP:	Yes
Year:	1999
Species/strain:	Chinese hamster ovary cells (CHO)
Concentrations tested:	Up to 901 ug/ml (this level meets the 10 mM max. recommended level)
Metabolic Activation:	Yes; Aroclor 1254-induced SD rat liver S9
Remarks:	The positive controls consisted of mitomycin-C and cyclophosphamide. Negative control was the test vehicle dimethylsulfoxide. A total of 200 cells per concentration were assessed.
Results	
Result:	No significant increases in cells with chromosomal aberrations, polyploidy, or endoreduplication were observed in the analyzed cultures at any concentration.
Cytotoxic concentration:	>901 ug/ml (no signs of toxicity were noted)
Precipitation concentration:	No precipitate was observed at the maximum concentration tested.
Genotoxic effects	
With activation:	Negative
Without activation:	Negative
Statistical methods:	Statistical analysis employed a Cochran-Armitage test for linear trends and Fisher's Exact Test to compare the percentage of cells with aberrations.
Remarks:	
Conclusions	Material was not genotoxic (did not induce any structural or numerical aberrations) under conditions of this assay.
Data Quality	
Reliability:	Reliable without restrictions
Remarks:	This was a well-documented OECD guideline study conducted under GLP assurances.
References	Covance Laboratories Inc., Vienna, VA; Study number: 23080-0-437OECD; January 3, 2002.
Other	

E. Developmental Toxicity

Test Substance	
Test substance:	MIPK
Remarks:	Purity was >99%
Method	
Method:	OECD:TG-421; USEPA: OPPTS 870.3550
GLP:	Yes
Year:	2001
Species/strain:	Rats/Sprague-Dawley CRL:CD®(SD)IGS BR
Sex:	Male and Female (12/sex/exposure level)
Route of exposure:	Inhalation, whole-body
Exposure levels:	0, 1, 2.5, and 5 mg/L
Actual exposure levels:	1.05 ± 0.046, 2.51 ± 0.144, and 5.17 ± 0.156 mg/L
Exposure period:	6 hrs/day
Frequency of treatment:	7 days/week
Control group and treatment:	Controls were exposed to filtered room air
Duration of test:	Males were exposed for 51 days while females were exposed for 35 to 48 days (through Day 19 of gestation). The exposure period was initiated two weeks prior to mating, and continued during the two-week mating period. The male rats continued exposure for a total exposure of 51 days and the females were exposed until Day 19 of gestation.
Remarks:	The study design included the additional endpoints of epididymal spermatozoan numbers and motility, and testicular spermatid head counts.
Results	
Maternal toxicity NOAEL:	Not Determined. Reductions in general activity levels were noted in all treated groups during the inhalation exposure. In addition, lower mean body weight gain and feed utilization was noted in all three treatment groups.
Repro./Develop. toxicity NOAEL:	1.0 mg/L. The effect noted in the 2.5 mg/L group was an increase in the number of dead pups/litter on lactation Day 0, an effect attributed to two of the twelve dams having three dead pups at birth. The mean percent Day 0 survival rate of the pups in the 2.5 mg/L group was 95.4%. Although this same effect was not noted in the 5.0 mg/L group, a reduced number of live pups/litter was noted on lactation Day 0 (mean of 11.6 versus 13.7 for the Control group) and an increased number of pups dying between lactation Days 0 to 4 (a 96.3% survival rate). The effect on lactation Day 0 (reduced number of live pups/litter) can be ascribed to one litter with 4 pups and the increased number of pups dying between lactation Days 0 to 4 is due to 4 pups dying in one litter during that time period. These differences were statistically significant due to the fact that the corresponding Control group had no litters with dead pups on lactation Day 0 and had no litters with any postnatal pup mortality.
Parental toxic responses:	Reductions in general activity levels during the inhalation exposure were noted the groups exposed to MIPK. Reductions in feed consumption, feed utilization, body weight and body weight gain were noted in the 2.5 and 5.0 mg/L groups. Lower mean body weight gain and feed utilization was noted at two time points for the male 1.0 mg/L group. Clinical signs noted in a groups exposed to MIPK included unkempt haircoat and saliva soaked perioral hair and periocular porphyrin discharges were noted in the 2.5 and 5.0 mg/L groups. There was no effect on fertility or other endpoints related to reproductive performance in any treatment group.

Postnatal toxic responses:	The only clinical signs considered related to exposure to the test article was a single pup in the 50 mg/L group that had loose, fluid-filled skin and hypothermia. The mean number of live pups/litter was reduced on lactation Day 0 and 4 for the 5.0 mg/L group. In addition, one litter in the 5.0 mg/L group had four pups die between Day 0 and 4. Two of twelve litters in the 2.5 mg/L group each had three dead pups on Day 0, with litter survival rates of 77-80%. Therefore, the number of dead pups/litter was increased for the 2.5 mg/L group although the pup survival rate was 95.4% (versus 100% in the Control group). The 1.0 mg/L group was comparable to the Control group.
Statistical Methods:	Homogeneity of data was evaluated using Bartlett's test ($p \leq 0.01$), one-way analysis of variance (ANOVA) ($p \leq 0.05$), and Dunnett's t-test ($p \leq 0.05$) to indicate statistical significance. When the variances of the means were not considered equal by the Bartlett's test ($p \leq 0.01$), the data were evaluated using a Kruskal-Wallis H-test ($p < 0.05$) followed by Mann-Whitney U-test ($p < 0.05$). The reproductive performance of the dams and the fertility and fecundity indices were evaluated in contingency tables, using a Chi-square test ($p < 0.05$). The total number of pups per litter (live and dead) and the total number of live pups per litter were evaluated using a linear regression model ($p < 0.05$).
Remarks:	MIPK did not affect the reproductive capacity of the adult animals in this study. Of the effects noted in the offspring, the reduced number of live pups/litter in the 5.0 mg/L is the most notable as the other effect noted at 5.0 mg/L (increased number of pups dying Day 0-4) was wholly dependent on one litter. The effect noted at 2.5 mg/L is of questionable significance given the propensity of dams to cannibalize and consume dead offspring. Finding three dead pups in two litters is unusual only in that dams usually consume the dead pups prior to them being found. These dead pups did not affect the mean number of live pups per litter or overall Day 0 survival rate (the mean value is also within the historical control range for this strain) and therefore this effect should be interpreted with caution.
Conclusions	Inhalation exposure to 1.0, 2.5, or 5.0 mg/L of MIPK resulted in significant toxicity to adult animals at all three exposure concentrations when compared to the control group. Fertility and other parameters related to reproductive capacity were unaffected in adult animals exposed to MIPK. The most significant effect (reduced mean number of pups/litter) on the offspring was noted at the 5.0 mg/L exposure level. The effect at 2.5 mg/L (increased number of dead pups/litter on Day 0) was of questionable significance as the number of live pups/litter and pup survival rate was unaffected. The 1.0 mg/L group was comparable to the Control group.
Data Quality Reliability: Remarks:	Reliable without restriction This was a well-documented OECD guideline study conducted under GLP assurances.
References	Reproduction/Developmental Toxicity Screening Test in the Rat. Toxicological Sciences Laboratory; Health and Environment Laboratories, Eastman Kodak Company, Rochester, NY; Study Number HAEL 2001-0250; Laboratory Project ID 200121, March 12, 2001.
Other	

F. Toxicity to Reproduction

Test Substance	
Test substance:	MIPK
Remarks:	Purity was >99%
Method	
Method:	OECD:TG-421; USEPA: OPPTS 870.3550
GLP:	Yes
Year:	2001
Species/strain:	Rats/Sprague-Dawley CRL:CD®(SD)IGS BR
Sex:	Male and Female (12/sex/exposure level)
Route of exposure:	Inhalation, whole-body
Exposure levels:	0, 1, 2.5, and 5 mg/L
Actual exposure levels:	1.05 ± 0.046, 2.51 ± 0.144, and 5.17 ± 0.156 mg/L
Exposure period:	6 hrs/day
Frequency of treatment:	7 days/week
Control group and treatment:	Controls were exposed to filtered room air
Duration of test:	Males were exposed for 51 days while females were exposed for 35 to 48 days (through Day 19 of gestation). The exposure period was initiated two weeks prior to mating, and continued during the two-week mating period. The male rats continued exposure for a total exposure of 51 days and the females were exposed until Day 19 of gestation.
Remarks:	The study design included the additional endpoints of epididymal spermatozoan numbers and motility, and testicular spermatid head counts.
Results	
Maternal toxicity NOAEL:	Not Determined. Reductions in general activity levels were noted in all treated groups during the inhalation exposure. In addition, lower mean body weight gain and feed utilization was noted in all three treatment groups.
Repro./Develop. toxicity NOAEL:	1.0 mg/L. The effect noted in the 2.5 mg/L group was an increase in the number of dead pups/litter on lactation Day 0, an effect attributed to two of the twelve dams having three dead pups at birth. The mean percent Day 0 survival rate of the pups in the 2.5 mg/L group was 95.4%. Although this same effect was not noted in the 5.0 mg/L group, a reduced number of live pups/litter was noted on lactation Day 0 (mean of 11.6 versus 13.7 for the Control group) and an increased number of pups dying between lactation Days 0 to 4 (a 96.3% survival rate). The effect on lactation Day 0 (reduced number of live pups/litter) can be ascribed to one litter with 4 pups and the increased number of pups dying between lactation Days 0 to 4 is due to 4 pups dying in one litter during that time period. These differences were statistically significant due to the fact that the corresponding Control group had no litters with dead pups on lactation Day 0 and had no litters with any postnatal pup mortality.
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Statistical Methods:	Homogeneity of data was evaluated using Bartlett's test ($p \leq 0.01$), one-way analysis of variance (ANOVA) ($p \leq 0.05$), and Dunnett's t-test ($p \leq 0.05$) to indicate statistical significance. When the variances of the means were not considered equal by the Bartlett's test ($p \leq 0.01$), the data were evaluated using a Kruskal-Wallis H-test ($p < 0.05$) followed by Mann-Whitney U-test ($p < 0.05$). The reproductive performance of the dams and the fertility and fecundity indices were evaluated in contingency tables, using a Chi-square test ($p < 0.05$). The total number of pups per litter (live and dead) and the total number of live pups per litter were evaluated using a linear regression model ($p < 0.05$).
Remarks:	MIPK did not affect the reproductive capacity of the adult animals in this study. Of the effects noted in the offspring, the reduced number of live pups/litter in the 5.0 mg/L is the most notable as the other effect noted at 5.0 mg/L (increased number of pups dying Day 0-4) was wholly dependent on one litter. The effect noted at 2.5 mg/L is of questionable significance given the propensity of dams to cannibalize and consume dead offspring. Finding three dead pups in two litters is unusual only in that dams usually consume the dead pups prior to them being found. These dead pups did not affect the mean number of live pups per litter or overall Day 0 survival rate (the mean value is also within the historical control range for this strain) and therefore this effect should be interpreted with caution.
Conclusions	Inhalation exposure to 1.0, 2.5, or 5.0 mg/L of MIPK resulted in significant toxicity to adult animals at all three exposure concentrations when compared to the control group. Fertility and other parameters related to reproductive capacity were unaffected in adult animals exposed to MIPK. The most significant effect (reduced mean number of pups/litter) on the offspring was noted at the 5.0 mg/L exposure level. The effect at 2.5 mg/L (increased number of dead pups/litter on Day 0) was of questionable significance as the number of live pups/litter and pup survival rate was unaffected. The 1.0 mg/L group was comparable to the Control group.
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Other	